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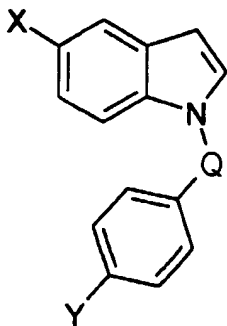
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(54) Title: **1H-INDOLE DERIVATIVES AS A HIGHLY SELECTIVE CYCLOOXYGENASE-2 INHIBITOR**



(I)

(57) Abstract: The present invention relates to a novel 1H-indole derivative having a struc-
ture of formula (I) and its pharmaceutically acceptable salts as a highly selective cyclooxy-
genase-2 inhibitor, wherein, X, Y, and Q are defined in this specification respectively.

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1H-INDOLE DERIVATIVES AS A HIGHLY SELECTIVE
CYCLOOXYGENASE-2 INHIBITOR

TECHNICAL FIELD

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The present invention relates to 1H-indole derivatives as a highly selective cyclooxygenase-2 inhibitor.

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BACKGROUND

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Most of non-steroid anti-inflammatory drugs represent actions such as anti-inflammation, ataralgesia, defervescence by inhibiting the enzymatic activity of cyclooxygenase or prostaglandin G/H synthase. In addition, they can suppress the uterine contraction induced by hormones and the cell proliferation in several kinds of cancers. First, only cyclooxygenase-1 was known to be found in cow as a constitutional enzyme. But recently, cyclooxygenase-2 is elucidated as an induced form. Cyclooxygenase-2 is identified to be discriminated clearly from cyclooxygenase-1 and can be provoked easily by mitogen, endotoxin, hormones, growth factors, cytokines and the like.

Prostaglandins have various pathological and physiological functions. Precisely, cyclooxygenase-1 as

a constitutional enzyme participates in the secretion of basic endogenous prostaglandin and plays an important role in physiological aspects such as stomach homeostasis, renal blood circulation and so on. On the other hand, cyclooxygenase-2 is induced by inflammatory factors, hormones, growth factors, cytokines and the like and thus plays an important role in pathological effects of prostaglandins. Therefore, selective inhibitors against cyclooxygenase-2 are expected to have no side effect on account of the functional mechanism compared with the anti-inflammatory drugs such as conventional non-steroid agents and to represent actions such as anti-inflammation, ataralgesia and defervescence. Furthermore, it is estimated to suppress the uterine contraction induced by hormones and the cell proliferation in several kinds of cancers. Especially, it probably has lesser side effects such as gastrointestinal toxicity, renal toxicity and the like. Also, it is assumed to prevent the synthesis of contractive prostanoids and thus inhibit the contraction of smooth muscle induced by the prostanoid. Hence, it can be applied usefully to treat a premature birth, dysmenorrhea, asthma and several diseases associated with eosinophilic leukocytes. Besides, it can be exploited widely to cure osteoporosis, glaucoma and athymia, which has been disclosed in a lot of references, especially the

usefulness of selective inhibitors against cyclooxygenase-2 (References: John Vane, " Towards a better aspirin " in *Nature*, Vol. 367, pp 215-216, 1994; Bruno Battistini, Regina Botting and Y. S. Bakhle, " COX-1 and COX-2; Toward the Development of More Selective NSAIDs " in *Drug News and Perspectives*, Vol. 7, pp 501-512, 1994; David B. Reitz and Karen Seibert, " Selective Cyclooxygenase Inhibitors " in *Annual Reports in Medicinal Chemistry*, James A. Bristol, Editor, Vol. 30, pp 179-188, 1995).

The selective inhibitors against cyclooxygenase-2 have been reported to have various structural forms. Among these, the diaryl heterocycle structure, namely a tricyclic system, has been studied most frequently and exploited to construct a lot of candidate substances. In this structure, it is essential that sulfonamide or methanesulfone group exist onto one phenyl group. The initial substance of such a structure is identified to be Dup697 (*Bioorganic and Medicinal Chemistry Letters*, Vol. 5, No. 18, p 2123, 1995). Then, as a derivative, SC-58635 (*Journal of Medicinal Chemistry*, Vol. 40, p 1347, 1997) having a pyrrazole structure, MK-966 (WO 95/00501) having a furanone structure and the like are disclosed.

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DISCLOSURE OF INVENTION

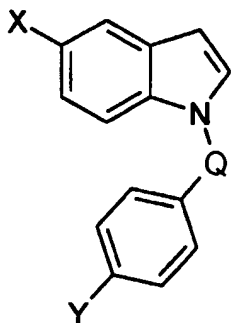
Based upon the above technical backgrounds, the inventors of the present invention have tried a lot in order to develop novel compounds as a highly selective cyclooxygenase-2 inhibitor. As a result, we have found that 1*H*-indole derivatives of formula 1 satisfied such a purpose and completed the present invention successfully.

Therefore, the object of the present invention is to provide 1*H*-indole derivatives of formula 1 and its pharmaceutically acceptable salts as depicted below.

Hereinafter, the present invention will be described more clearly.

The present invention relates to 1*H*-indole derivatives of formula 1 and its pharmaceutically acceptable salts.

<Formula 1>



Wherein, --- is a double bond or a single bond,
X is NO₂, NH₂, or -NHSO₂R wherein R represents

hydrogen or C₁-C₃-alkyl,

Y is hydrogen, halogen, C₁-C₃-alkyl substituted or not substituted by halogen, NO₂, NH₂, OH, OMe, CO₂H, or CN,

5 Q is C=O, C=S, or CH₂.

The compound of the present invention can exist as a pharmaceutically acceptable salt form, wherein the pharmaceutically acceptable salt means a nontoxic salt containing organic salt and inorganic salt and accepted
10 pharmaceutically. The inorganic salt consists of aluminum, ammonium, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc and the like and preferably, ammonium, calcium, magnesium, potassium, sodium. The organic salt consists of
15 primary-, secondary- or tertiary- amines, naturally substituted amines, cyclic amines, modified salts prepared through a basic ion exchange resin and the like. Preferably, the organic salt can be selected among arginine, betain, caffeine, colin, N,N-
20 dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, N-methylglucamine, glucamine, glucosamine, histidine, hydropamine, N-(2-
25 hydroxyethyl)piperidine, N-(2-hydroxyethyl)pyrrolidine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resin, procain,

purine, teobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

Besides, the compound of the present invention can be a salt form of nontoxic acids containing the organic acid and the inorganic acid and accepted pharmaceutically, in case that it be basic. Preferably, the acid can be adopted among acetic acid, adipic acid, aspartic acid, 1,5-naphthalenedisulfonic acid, benzenesulfonic acid, benzo acid, camposulfonic acid, citric acid, 1,2-ethanedisulfonic acid, ethanesulfonic acid, ethylenediaminetetraacetic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, hydriodic acid, hydrobromic acid, hydrochloric acid, icethionic acid, lactic acid, maleic acid, malic acid, mandelic acid, methanesulfonic acid, nicotinic acid, 2-naphthalene disulfonic acid, nitric acid, oxalic acid, pantoic acid, pantothenic acid, phosphoric acid, pivalic acid, propionic acid, salicylic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid, 10-undecenoic acid and the like and more preferably, among succinic acid, hydrobromic acid, hydrochloric acid, maleic acid, methanesulfonic acid, phosphoric acid, sulfuric acid, tartaric acid and the like.

Preferably, the compound of the present invention of formula 1 as a selective inhibitor against cyclooxygenase-2 is that X is NO_2 , NH_2 , or -

NHSO₂CH₃, Y is hydrogen, halogen, C₁-C₃-alkyl, or OMe, and Q is C = O or CH₂.

For preferred embodiments of the present invention, the compounds of formula 1 will be described more clearly as follows:

- 1-benzoyl-5-nitro-1*H*-indole;
- 1-benzyl-5-nitro-1*H*-indole;
- 1-(4-fluoro-benzyl)-5-nitro-1*H*-indole;
- 1-(4-methoxy-benzyl)-5-nitro-1*H*-indole;
- 10 1-(4-isopropyl-benzyl)-5-nitro-1*H*-indole;
- 1-benzoyl-5-amino-1*H*-indole;
- N-(1-benzyl-1*H*-indole-5-yl)-methanesulfonamide;
- N-[1-(4-fluoro-benzyl)-1*H*-indole-5-yl]-methanesulfonamide;
- 15 N-(1-benzoyl-1*H*-indole-5-yl)-methanesulfonamide;
- 1-benzyl-5-nitro-2,3-dihydro-1*H*-indole;
- N-(1-benzyl-2,3-dihydro-1*H*-indole-5-yl)-methanesulfonamide; and
- N-(1-benzoyl-2,3-dihydro-1*H*-indole-5-yl)-methansulfonamide.
- 20

On the other hand, the compounds of formula 1 in the present invention can be prepared by performing the procedures as illustrated below.

25 However, the process for preparing the compounds of the present invention will not be restricted to following descriptions, especially in reaction solvents,

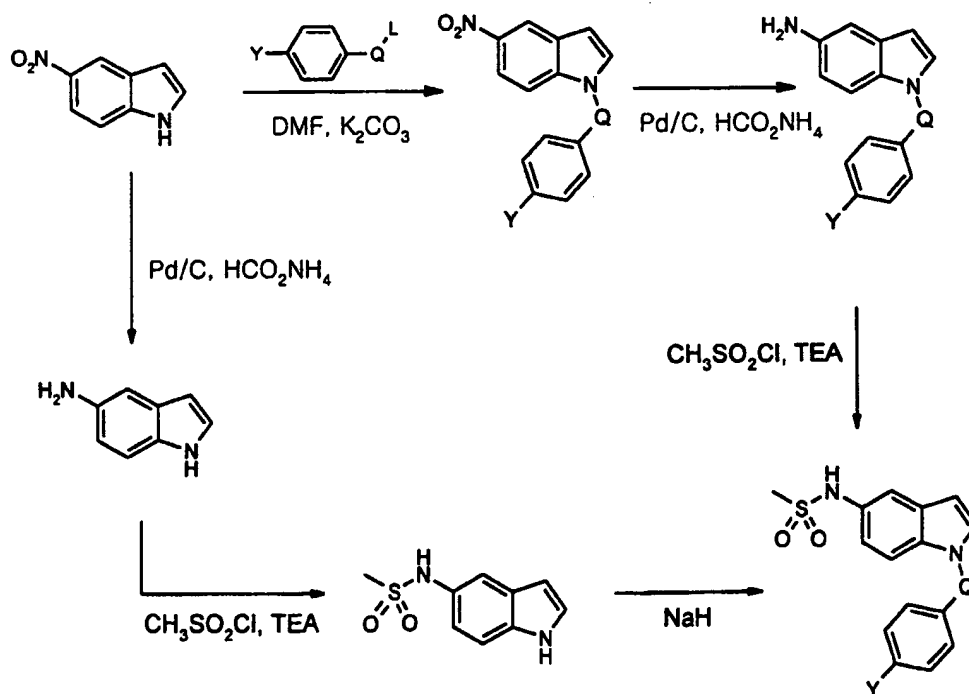
bases, amounts of used reactants and the like.

Moreover, the compound of the present invention also can be prepared by exploiting and combining various synthetic methods described in the present specification or disclosed in other references of those skilled in this arts with a coordinate and arbitrary mode.

Those skilled in the art will appreciate that the conceptions and specific embodiments disclosed in the foregoing description may be readily utilized as a basis for modifying or designing other embodiments.

Concretely, the compound of formula 1 in the present invention can be prepared as illustrated schematically in following reaction formula 1.

15 <Reaction Formula 1>



Wherein, ---, X, Y, and Q are defined above,

L is halogen.

As demonstrated in the above reaction formula 1, the compound of the present invention can be prepared through 2 pathways from 5-nitroindole or 5-nitroindoline as initial material. Namely, benzoyl group or benzyl group are introduced to a nitrogen atom included in the parent nucleus first and then, methanesulfonyl group is inserted to an amine group on 5-location (method 1). On the other hand, methanesulfonyl group is adopted to an amine group on 5-location of parent nucleus first, and then benzoyl group or benzyl group are introduced later (method 2).

A detailed description on preparing the compound of the present invention by the above method (1) is as follows.

The reaction of 5-nitroindole or 5-nitroindoline with benzoylhalide or benzylhalide derivatives should be specifically accomplished under the presence of a base. Concretely, the reaction is performed at the range of room temperature ~ 80°C by using dimethylformamide. At this moment, the organic base can be selected among triethylamine, trimethylamine, tripropylamine, pyridine, imidazole, and the like, while the inorganic base can be selected among sodiumacetate, sodium hydroxide, sodium hydride, potassium hydroxide, sodium carbonate, potassium

carbonate, and the like. More preferably, potassium carbonate can be adopted.

5 The reaction reducing from nitro to amine is performed under the presence of palladium/ carbon and ammonium formate as a catalyst at the range of room temperature ~ 80°C by using a single or mixed solvent selected among tetrahydrofuran, diethylether, dimethoxyethane, ethylacetate, dichloromethane, methanol, and ethanol.

10 The reaction forming sulfonamide is accomplished as follows: amine and mesyl chloride is reacted under the presence of a base such as triethylamine, trimethylamine, tripropylamine, pyridine, imidazole, and the like by using a solvent selected among
15 tetrahydrofuran, diethylether, dimethoxyethane, ethylacetate, dichloromethane, methanol, ethanol and the like. Preferably, it should be performed at the range of 0 ~ 50°C and more preferably, at a low temperature in between 5 ~ 10°C.

20 On the other hand, a detailed description on preparing the compound of the present invention by the above method (2) is as follows.

25 The reduction of 5-nitroindole or 5-nitroindoline as initial material is performed under the same condition with the above method (1) which exploits palladium/ carbon as a catalyst.

Then, the formation of sulfonamide of 5-

aminoindole or 5-aminoindoline prepared thereby is accomplished as follows: amine and mesyl chloride is reacted under the presence of a base such as triethylamine, trimethylamine, tripropylamine, pyridine, imidazole, and a solvent selected among tetrahydrofuran, diethylether, dimethoxyethane, ethylacetate, dichloromethane, methanol, and ethanol. Preferably, it should be performed at the range of -30°C ~ room temperature and more preferably, at a low temperature in between -20 ~ -10°C .

The resulting sulfonamide compound will be reacted with bezoylhalide or benzylhalide derivatives through the following procedure. The reaction solvent can be a non-reactive solvent such as dichloromethane, diethylether, tetrahydrofuran, and the like. At this moment, the reaction temperature should be preferably at the range of -30 ~ 20°C and more preferably, at a low temperature in between -20 ~ -10°C . A base should be exploited for this reaction, which can be selected among triethylamine, trimethylamine, tripropylamine, pyridine, imidazole and the like as an organic base and among sodium acetate, sodium hydroxide, sodium hydride, potassium hydroxide, sodium carbonate, potassium carbonate and the like as an inorganic base, more preferably sodium hydride.

After completing the reaction, the resulting products can be processed through a common treatment

such as chromatography, re-crytallization and the like so as to be separated and purified.

The compound of the present invention depicted in formula 1 has an activity for the selective inhibition
5 against cyclooxygenase-2 and thus can be utilized as an enzymatic inhibitor. The compound of formula 1 having a selective inhibitor against cyclooxygenase-2 can be a substitute for conventional non-steroid anti-inflammatory drugs and especially the compound is
10 useful in patients suffering from peptic ulcer, gastritis, partial enteritis, ulcerative colitis, diverticulitis, gastrointestinal haemorrhagia, hypoprothrombinemia and the like as substitute drugs improved in side effects of conventional non-steroid
15 anti-inflammatory drugs. Besides, it is expected to treat inflammatory diseases such as osteoarthritis, rheumatoid arthritis and the like effectively.

The compound of the present invention can be administered in a single dose or in separated doses,
20 depending upon clinical purposes. The specific dosage for patients will vary, depending upon factors such as a sort of drug compound, body weight, sex, physical condition, diet, administration period, administration method, discharge ratio, drug composition and severity
25 of diseases and the like.

The compound of the present invention can be administered as an oral, a local, a parenteral

(subcutaneous, venous and muscular silinge or injection), an inhalational or a rectal drug. In case that these are prepared to a pharmaceutical drug, one or more commonly used vehicles, methods for the preparation and the like can be adopted properly from prior arts widely reported to those skilled.

In order to attain the desired purpose of clinical administration, the active compound of formula 1 in the present invention can be administered coincidentally by combining more than one component of other commercial drugs.

However, the pharmaceutical drugs containing the compound of the present invention is not limited to forms described above, if it has a purpose for inhibiting cyclooxygenase-2 selectively. All kinds of drugs useful for the enzymatic inhibition can be within the scope of the present invention.

MODES FOR CARRYING OUT THE INVENTION

20

Practical and presently preferred embodiments of the present invention are illustrative as shown in the following Examples.

However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

<Reference Example 1> Preparation of (1H-indole-5-yl)-
amine

5 5-nitroindole (1.0g, 6.17 mmol) was dissolved in
methanol (10ml) and anhydrous tetrahydrofuran (10ml) at
room temperature and then, palladium/ carbon (10%) of a
catalytic amount and ammonium formate (2.0g, 31.7
mmol) were added to be stirred slowly at room
10 temperature for 30 minutes. After completing the
reaction, the reacting solution was filtered through
celite, washed with methanol, concentrated under
reduced pressure and then, dropped a silica gel short
column. Afterward, the residue was concentrated again
15 under reduced pressure and triturated with isooctane.
As a result, the present compound (0.45g, productive
yield 55%) was obtained as a solid phase.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.55 (br s, 2H), 6.35 (s,
1H), 6.65 (d, $J = 8\text{Hz}$, 1H), 6.95 (s, 1H), 7.10-7.15 (m,
20 1H), 7.20 (d, $J = 8\text{Hz}$, 1H), 7.95 (br s, 1H)
melting point : 126°C

<Reference Example 2> Preparation of N-(1H-indole-5-
yl)-methansulfonamide

25

(1H-indole-5-yl)-amine (50mg, 0.38mmol) was
dissolved in dichloromethane (1.0ml) at -20°C and

trimethylamine (0.063ml, 0.45mmol) and mesyl chloride (0.032ml, 0.45mmol) were added to be slowly stirred at room temperature for 30 minutes. After completing the reaction, water (5ml) and dichloromethane (5ml) were added additionally and dichloromethane layer was separated. Afterward, the resulting solution was washed with brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and then purified by performing a flash column chromatography (an eluent: ethyl acetate/n-hexane = 1/2, v/v). As a result, the present compound (30mg, productive yield 38%) was obtained.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.95 (s, 3H), 6.25 (br s, 1H), 6.55 (s, 1H), 7.10 (d, $J = 8\text{Hz}$, 1H), 7.25-7.30 (m, 1H), 7.35 (d, $J = 8\text{Hz}$, 1H), 7.5 (s, 1H)

<Reference Example 3> Preparation of N-(2,3-dihydro-1H-indole-5-yl)-methansulfonamide

5-nitroindoline (100mg, 0.61mmol) was dissolved in methanol (2ml) and tetrahydrofuran (2ml). Ammonium formate (192mg, 3.05mmol, 5 equivalent) and palladium/carbon (10%) in a catalytic amount were added at room temperature and refluxed at 40°C for ten minutes. After completing the reaction, the reacting solution was filtrated through celite and concentrated under reduced pressure. Afterward, water (5ml) was added to

the residue, extracted consecutively 4 times with ethyl acetate (10ml), dried over anhydrous magnesium sulfate, concentrated under reduced pressure and then dried completely under a high-degree vacuum. The obtained
5 compound, namely (2,3-dihydro-1*H*-indole-5-yl)-amine, was dissolved in dichloromethane (5ml). Then, trimethylamine (0.063ml, 0.45mmol) was added to be cooled to -20°C and mesyl chloride (0.035ml, 0.45mmol) was added to be stirred for 30 minutes at the same
10 temperature. Water (5ml) was added to separate dichloromethane solution, dried over anhydrous magnesium sulfate, purified through a flash column chromatography (an eluent: ethyl acetate/n-hexane = 2/1, v/v) and then triturated with isooctane. As a result,
15 the present compound (60mg, productive yield 47%) was obtained as a white solid.

¹H-NMR (400 MHz, DMSO-d₆) δ 2.00 (s, 3H), 3.15 (t, J = 8Hz, 2H), 3.95 (t, J = 8Hz, 2H), 7.25 (d, J = 8Hz, 1H), 7.45-7.60 (m, 4H), 7.80 (s, 1H), 7.95 (d, J = 8Hz, 1H)
20

<Example 1> Preparation of 1-benzoyl-5-nitro-1*H*-indole

25 5-nitroindole (50mg, 0.31mmol) and potassium carbonate (128mg, 0.93mmol) were suspended in dimethylformamide (1.0ml). Then, benzoyl chloride

(0.04ml, 0.345mmol) was added and stirred at room temperature for 2 hours. After completing the reaction, water and ethylacetate (respectively 5ml) were added to extract, washed with brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and then purified through a flash column chromatography (an eluent: ethyl acetate/n-hexane = 1/1, v/v). As a result, the present compound (35mg, productive yield 43%) was obtained.

¹H-NMR (400 MHz, CDCl₃) δ 6.80 (d, J = 3Hz, 1H), 7.50 (d, J = 3Hz, 1H), 7.55-7.70 (m, 3H), 7.80 (d, J = 8Hz, 2H), 8.25-8.30 (m, 1H), 8.50 (d, J = 9Hz, 1H), 8.55 (s, 1H)

<Example 2> Preparation of 1-benzyl-5-nitro-1H-indole

The reaction was performed through a same method with Example 1, except exploiting benzyl bromide (0.04ml, 0.366mmol) instead of benzoylchloride. As a result, the present compound (40mg, productive yield 51%) was obtained.

¹H-NMR (400 MHz, CDCl₃) δ 5.35 (s, 2H), 6.75 (t, J = 2Hz, 1H), 7.10-7.15 (m, 2H), 7.25-7.40 (m, 5H), 8.10 (d, J = 9Hz, 1H), 8.65 (d, J = 2Hz, 1H)

melting point : 103 ~ 104°C

<Example 3> Preparation of 1-(4-fluoro-benzyl)-5-nitro-1H-indole

5 The reaction was performed through a same method with Example 1, except exploiting 4-fluorobenzyl bromide (0.04ml, 0.342mmol) instead of benzoylchloride. As a result, the present compound (55mg, productive yield 66%) was obtained.

10

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.35 (s, 2H), 6.75 (d, $J = 3\text{Hz}$, 1H), 7.00-7.15 (m, 4H), 7.25-7.30 (m, 2H), 8.10 (d, $J = 9\text{Hz}$, 1H), 8.60 (d, $J = 2\text{Hz}$, 1H)

melting point : 114 ~ 115°C

15

<Example 4> Preparation of 1-(4-methoxy-benzyl)-5-nitro-1H-indole

20 The reaction was performed through a same method with Example 1, except exploiting 4-methoxybenzyl bromide (0.046ml, 0.339mmol) instead of benzoylchloride. As a result, the present compound (60mg, productive yield 69%) was obtained.

25 $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 3.80 (s, 3H), 5.30 (s, 2H), 6.70 (d, $J = 3\text{Hz}$, 1H), 6.85 (d, $J = 8\text{Hz}$, 2H), 7.05

(d, J = 8Hz, 2H), 7.25 (d, J = 3Hz, 1H), 7.30 (d, J = 9Hz, 1H), 8.10 (d, J = 9Hz, 1H), 8.60 (s, 1H)

melting point : 110 ~ 111°C

5 **<Example 5> Preparation of 1-(4-isopropyl-benzyl)-5-nitro-1H-indole**

The reaction was performed through a same method with Example 1, except exploiting 4-isopropylbenzyl bromide (0.056ml, 0.339mmol) instead of benzoylchloride. As a result, the present compound (65mg, productive yield 72%) was obtained.

¹H-NMR (400 MHz, CDCl₃) δ 1.20 (s, 3H), 1.25 (s, 3H), 2.90-2.95 (m, 1H), 5.30 (s, 2H), 6.75 (d, J = 3Hz, 1H), 7.05 (d, J = 8Hz, 2H), 7.20 (d, J = 8Hz, 2H), 7.30 (d, J = 3Hz, 1H), 7.35 (d, J = 9Hz, 1H), 8.05 (d, J = 9Hz, 1H), 8.60 (s, 1H)

melting point : 120 ~ 121°C

20 **<Example 6> Preparation of 1-benzoyl-5-amino-1H-indole**

1-benzoyl-5-nitro-1H-indole (50mg) was dissolved in a mixed solvent with methanol (2ml) and tetrahydrofuran (2ml), and ammonium formate of an excess amount and palladium/ carbon (10%) of a catalytic amount were added. The reacted solution was

stirred at around 30°C for 30 minutes to complete the reduction, filtered through celite and then, concentrated under reduced pressure. Afterward, the residue was dissolved again in ethylacetate (10ml),
5 washed with water and brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure and then, triturated with isooctane and isopropylether. As a result, the present compound (25mg, productive yield 56%) was obtained as a solid.

10

¹H-NMR (400 MHz, CDCl₃) δ 3.70 (br s, 2H), 6.45 (d, J = 4Hz, 1H), 6.80-6.85 (m, 1H), 6.85 (s, 1H), 7.20 (d, J = 4Hz, 1H), 7.40-7.60 (m, 3H), 7.70 (d, J = 9Hz, 2H), 8.20 (d, J = 9Hz, 1H)

15

<Example 7 >N-(1-benzyl-1H-indole-5-yl)-methanesulfonamide

1-benzyl-5-nitro-1H-indole (50mg, 0.19mmol)
20 was dissolved in tetrahydrofuran (1ml) and methanol (1ml), and ammonium formate of an excess amount and palladium/ carbon (10%) of a catalytic amount were added. The solution was stirred at around 30°C for 30 minutes to complete the reduction, filtrated through
25 celite, concentrated under reduced pressure, dissolved again in dichloromethane (10ml), and then washed with water and brine. After drying the resulting solution

over anhydrous magnesium sulfate, dichloromethane solution containing amine compound (1-benzyl-5-amino-1*H*-indole) was obtained. Mesyl chloride (0.015ml, 0.19mmol) and triethylamine (0.028ml, 0.20mmol) were
5 added to the above obtained solution and stirred at room temperature for 2 hours to complete the reaction. After adding 2N-hydrochloric acid solution (10ml) to separate layers, dichloromethane solution was induced, washed by using water and brine, dried over anhydrous
10 magnesium sulfate, concentrated under reduced pressure, and then triturated with isooctane and isopropylether. As a result, the present compound (34mg, productive yield 34%) was obtained as a solid.

15 ¹H-NMR (400 MHz, CDCl₃) δ 2.95 (s, 3H), 5.30 (s, 2H), 6.25 (s, 1H), 6.55 (s, 1H), 7.00-7.35 (m, 8H), 7.55 (s, 1H)

Mass (FAB) 300.0 (M +), 601.1 (2M + 1)

melting point : 153 ~ 154°C

20

<Example 8> Preparation of N-[1-(4-fluoro-benzyl)-1*H*-indole-5-yl]-methansulfonamide

1-(4-fluoro-benzyl)-5-nitro-1*H*-indole (50mg,
25 0.16mmol) was dissolved in tetrahydrofuran (1ml) and methanol (1ml), and ammonium formate of an excess amount and palladium/ carbon (10%) of a catalytic

amount were added. The solution was stirred at around 30°C for 1 hour to complete the reduction, filtered through celite, concentrated under reduced pressure, dissolved again in dichloromethane (10ml), and then
5 washed with water and brine. After drying the resulting solution over anhydrous magnesium sulfate, dichloromethane solution containing amine compound (1-(4-fluoro-benzyl)-5-amino-1*H*-indole) was obtained. Mesyl chloride (0.012ml, 0.16mmol) and triethylamine
10 (0.022ml, 0.16mmol) were added to the above obtained solution and stirred at room temperature for 2 hours to complete the reaction. After adding 2*N*-hydrochloric acid solution (10ml) to separate layers, dichloromethane solution was induced, washed with water
15 and brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and then triturated with isooctane and isopropylether. As a result, the present compound (30mg, productive yield 51%) was obtained as a solid.

20

¹H-NMR (400 MHz, CDCl₃) δ 2.95 (s, 3H), 5.25 (s, 2H), 6.35 (s, 1H), 6.50-6.55 (m, 1H), 6.95-7.25 (m, 7H), 7.55 (s, 1H)

melting point : 96 ~ 97°C

25

<Example 9> Preparation of N-(1-benzoyl-1*H*-indole-5-yl)-methanesulfonamide

1-benzoyl-5-amino-1*H*-indole (25mg, 0.106mmol) was dissolved in dichloromethane (1.0ml) at room temperature and mesyl chloride (0.01ml, 0.116mmol) and triethylamine (0.016ml, 0.115mmol) were added. The solution was stirred at room temperature for 30 minutes to complete the reducing reaction. After pouring water (2ml), dichloromethane layer was separated, washed with brine, dried over anhydrous magnesium sulfate and then, purified through flash column chromatography (an eluent: ethyl acetate/n-hexane = 1/2, v/v). As a result, the present compound (20mg, productive yield 60%) was obtained.

¹H-NMR (400 MHz, CDCl₃) δ 3.00 (s, 3H), 6.40 (s, 1H), 6.60 (d, J = 4Hz, 1H), 7.20 (d, J = 8Hz, 1H), 7.35 (d, J = 4Hz, 1H), 7.50-7.65 (m, 4H), 7.75 (d, J = 8Hz, 2H), 8.40 (d, J = 8Hz, 1H)

Mass (FAB) 314 (M +), 629 (2M + 1)

melting point : 123 ~ 125°C

<Example 10> Preparation of 1-benzyl-5-nitro-2,3-dihydro-1*H*-indole

Under the presence of nitrogen, 5-nitroindolin (50mg, 0.30mmol) was dissolved in dimethylformamide (2ml) at room temperature and benzyl bromide (0.04ml.

0.34mmol) and potassium carbonate (0.126ml, 3.0 equivalent) were added and stirred at room temperature for 48 hours. After completing the reaction, water and ethyl acetate (respectively 5ml) were added to separate layers, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. Finally, the residue was purified through flash column chromatography (an eluent: ethyl acetate/n-hexane = 1/4, v/v). As a result, the present compound (45mg, productive yield 58%) was obtained.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 3.10 (t, $J = 9\text{Hz}$, 2H), 3.65 (t, $J = 9\text{Hz}$, 2H), 4.45 (s, 2H), 6.35 (d, $J = 9\text{Hz}$, 1H), 7.25-7.45 (m, 5H), 7.90 (s, 1H), 8.05-8.10 (m, 1H)
melting point : $73 \sim 74^\circ\text{C}$

<Example 11> Preparation of N-(1-benzyl-2,3-dihydro-1H-indole-5-yl)-methanesulfonamide

1-benzyl-5-nitro-2,3-dihydro-1H-indole (100mg, 0.39mmol) was dissolved in tetrahydrofuran (1ml) and methanol (1ml), and ammonium formate (124mg, 1.96mmol, 5 equivalent) and palladium carbon (10%) of a catalytic amount were added. Then, the solution was stirred at 40°C for 10 minutes to complete the reduction. After completing the reaction, the solution was filtered through celite, concentrated under reduced pressure,

dissolved again in ethyl acetate (10ml), washed with water and salt solution, dried over anhydrous magnesium sulfate, concentrated again under reduced pressure and then, dried completely under a high-degree vacuum.

5 Afterward, the obtained residue was dissolved with dichloromethane (2.0ml), cooled to 0°C, blended with triethylamine (0.055ml, 0.39mmol) and mesyl chloride (0.031ml, 0.40mmol) and then, stirred at the same temperature for 30 minutes to complete the reaction.

10 After pouring water (2.0ml) again at room temperature, dichloromethane layer was separated, washed with brine, dried over anhydrous magnesium sulfate, and concentrated. Finally, the residue was purified through flash column chromatography (an eluent: ethyl acetate/n-hexane = 1/2, v/v). As a result, the present

15 compound (90mg, productive yield 76%) was obtained.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.95 (t, $J = 8\text{Hz}$, 2H), 3.35 (t, $J = 8\text{Hz}$, 2H), 4.25 (s, 2H), 6.00 (s, 1H), 6.40

20 (d, $J = 8\text{Hz}$, 1H), 6.90 (d, $J = 8\text{Hz}$, 1H), 7.05 (s, 1H), 7.20-7.35 (m, 5H)

Mass (FAB) 302 (M +), 605 (2M + 1)

melting point : 133 ~ 134°C

25 <Example 12> N-(1-benzoyl-2,3-dihydro-1H-indole-5-yl)-methanesulfonamide

N-(2,3-dihydro-1*H*-indole-5-yl)-
methanesulfonamide (20mg, 0.095mmol) was dissolved in
anhydrous dichloromethane (3ml), sodium hydride
(0.010g, 50% in oil) was added and then,
5 benzoylchloride (0.011ml, 0.095mmol) was added at a
temperature under -20°C. The resulting solution was
stirred at the same temperature for 1 hour, stirred
again at room temperature for 24 hours to complete
the reaction. After pouring water (3ml),
10 dichloromethane layer was separated, washed with
brine, dried over anhydrous magnesium sulfate and
then, concentrated under reduced pressure. Afterward,
the residue was purified through flash column
chromatography (an eluent: ethyl acetate/n-hexane =
15 1/1, v/v) and triturated with isooctane. As a result,
the present compound (15mg, productive yield 50%) was
obtained as a solid.

¹H-NMR (400 MHz, CDCl₃) δ 2.90 (s, 3H), 3.20 (t,
20 J = 8Hz, 2H), 4.00 (t, J = 8Hz, 2H), 7.20 (d, J = 8Hz,
1H), 7.40 (d, J = 8Hz, 1H), 7.45-7.60 (m, 3H), 7.80 (m,
2H), 7.90 (d, J = 8Hz, 2H)

Mass (FAB) 317.1(M + 1)

25 <Experimental Example> The activity of selective
inhibition against cyclooxygenase-2

(1) Experimental procedure

In order to investigate the activity of the present compound for the selective inhibition against cyclooxygenase-2 enzyme pharmacologically, the enzymatic activities inhibiting cyclooxygenase-1 and cyclooxygenase-2 were measured quantitatively.

First of all, the cyclooxygenase-1 was examined through the following procedure.

Peritoneal fluid in which macrophages were suspended was extracted from a mouse peritoneal cavity and centrifuged at 4°C, 1,000 rpm for 2 minutes. Then, the supernatant was removed, suspended with 20ml of incomplete RPMI medium [PC/SM (penicilin/streptomycin)] and again centrifuged under the same condition. In addition, the reactant was washed twice and then the cell pellet was suspended with 10 ml of incomplete RPMI 1640 medium so as to prepare a cell suspension. Then, the cell number was calculated with the hemocytometer and adjusted to reach 1×10^6 cells/ml of cell concentration in the final cell suspension. 100 μ l of the resulting suspension was transferred into each well of 96-well plate and left at 37°C in 5% CO₂ with the incubator for about 2 hours in order to attach macrophages. The attached macrophage was washed twice by using PBS buffer, treated to experimental samples in a proper concentration and then blended with 3% FBS-

RPMI 1640 medium so as to adjust the total volume reaching 200 μ l. The resulting cell was cultivated in the incubator at 37°C in 5% CO₂ for about 12 ~ 16 hours. Then, arachidonic acid was added, adjusting to 10 μ M of a final concentration and incubated at 37°C for more 10 minutes and the supernatant of the reacted solution (~180 μ l) was recovered to finish the reaction. In order to quantitate the amount of PGE₂ in the samples, the ELISA method recommended from Cayman Chemical company was exploited and the obtained results was used to estimate the inhibition ratio (%) of each compound against cyclooxygenase-1.

Second, the cyclooxygenase-2 was examined through the following procedure.

Peritoneal fluid suspended with macrophages was extracted from a mouse peritoneal cavity and centrifuged at 4°C, 1,000 rpm for 2 minutes. Then, the supernatant was removed, suspended using incomplete RPMI medium [PC/SM (penicillin/streptomycin)] and again centrifuged under the same condition. In addition, the reactant was washed twice and then the cell pellet was suspended with 10 ml of incomplete RPMI 1640 medium so as to prepare a cell suspension. Then, the cell number was calculated with the hemocytometer and adjusted to reach 1×10^6 cells/ml of cell concentration in the final cell suspension. The resulting suspension was treated with aspirin, adjusting 500 μ M of final

concentration and transferred into each well of 96-well plate in 100 μ l respectively. Again, it was left at 37°C in 5% CO₂ in the incubator for about 2 hours in order to attach macrophages. The attached macrophage was washed twice by using PBS buffer, treated to experimental samples in a proper concentration and then blended with 3% FBS-RPMI 1640 medium containing 10 μ g/ml of LPS in each well. The resulting cell was cultivated in the incubator at 37°C in 5% CO₂ for about 12 ~ 16 hours. Then, arachidonic acid was added, adjusting to 10 μ M of a final concentration and incubated at 37°C for more 10 minutes and the supernatant of the reacted solution (~ 180 μ l) was recovered to finish the reaction. In order to quantitate the amount of PGE2 in the samples, the ELISA method recommended from Cayman Chemical company was exploited and the obtained results was used to estimate the inhibition ratio (%) of each compound against cyclooxygenase-2.

20

(2) Experimental results

The experimental results were demonstrated in **Table 1** as follows.

<Table 1>

Inhibitory effects of cyclooxygenase (COX) (unit: % inhibition)

Examples	COX-1			COX-2		
Concentration	30 μ M	10 μ M	3 μ M	300 nM	100 nM	30 nM
SC-58635 (standard substance)	81.3	66.5	64.3	73.0	59.9	51.2
1	45.8	40.7	33.2	~ 0	~ 0	~ 0
2	80.4	68.7	56.7	22.0	20.7	15.7
3	74.6	64.4	60.4	70.2	58.8	50.1
4	80.1	71.1	60.3	81.5	69.9	55.4
5	54.3	47.1	39.9	61.4	55.4	51.2
6	64.8	57.3	52.3	54.9	46.6	33.4
7	56.4	44.1	30.0	76.8	70.6	59.8
8	53.9	32.3	7.6	29.6	28.6	22.1
9	42.1	31.1	22.8	30.1	25.5	20.4

5

In vitro experiments were observed to measure the inhibitional ratios against cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Consequently, in case of the compound of Example 7, N-(1-benzyl-1H-indole-5-yl)-methanesulfonamide, the inhibition effect against cyclooxygenase-2 was identified to be more excellent than a comparative substance and coincidentally, the inhibition effect against cyclooxygenase-1 be in much lower level than a comparative substance. That is to say, the selectivity of cyclooxygenase-2 is confirmed

10

15

to be better than any other substances, which proves the structural efficacy of 1H-indole derivatives in the present invention.

5

INDUSTRIAL APPLICABILITY

As demonstrated and confirmed above, the novel compound of 1H-indole derivative is a substitute drug improved in side effects of conventional non-steroids anti-inflammatory drug and is useful for patients suffering from peptic ulcer, gastritis, partial enteritis, ulcerative colitis, diverticulitis, gastrointestinal haemorrhagia, hypoprothrombinemia and the like. Besides, it is expected to treat inflammatory diseases such as osteoarthritis, rheumatoid arthritis and the like effectively.

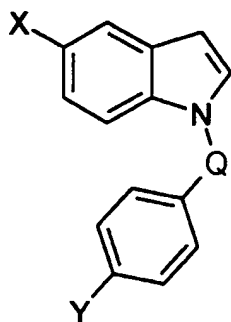
Those skilled in the art will appreciate that the conceptions and specific embodiments disclosed in the foregoing description may be readily utilized as a basis for modifying or designing other embodiments for carrying out the same purposes of the present invention.

Those skilled in the art will also appreciate that such equivalent embodiments do not depart from the spirit and scope of the invention as set forth in the appended claims.

What is claimed is:

1. A compound of formula 1 and its pharmaceutically acceptable salts:

5 <Formula 1>



Wherein, --- is a double bond or a single bond,

X is NO₂, NH₂, or -NHSO₂R wherein R represents hydrogen or C₁-C₃-alkyl,

10 Y is hydrogen, halogen, C₁-C₃-alkyl substituted or not substituted by halogen, NO₂, NH₂, OH, OMe, CO₂H, or CN,

Q is C=O, C=S, or CH₂.

15 2. The compound of formula 1 according to claim 1, wherein X is NO₂, NH₂, or -NHSO₂CH₃, Y is hydrogen, halogen, C₁-C₃-alkyl, or OMe, and Q is C=O or CH₂.

20 3. The compound according to claim 1, wherein said compound of formula 1 is selected from a group consisting of:

- 1-benzoyl-5-nitro-1*H*-indole;
1-benzyl-5-nitro-1*H*-indole;
1-(4-fluoro-benzyl)-5-nitro-1*H*-indole;
1-(4-methoxy-benzyl)-5-nitro-1*H*-indole;
5 1-(4-isopropyl-benzyl)-5-nitro-1*H*-indole;
1-benzoyl-5-amino-1*H*-indole;
N-(1-benzyl-1*H*-indole-5-yl)-methanesulfonamide;
N-[1-(4-fluoro-benzyl)-1*H*-indole-5-yl]-
methanesulfonamide;
10 N-(1-benzoyl-1*H*-indole-5-yl)-methanesulfonamide;
1-benzyl-5-nitro-2,3-dihydro-1*H*-indole;
N-(1-benzyl-2,3-dihydro-1*H*-indole-5-yl)-
methanesulfonamide; and
N-(1-benzoyl-2,3-dihydro-1*H*-indole-5-yl)-
15 methansulfonamide.

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/KR02/01843

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 209/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 209/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
stn on the web

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2345486 A (GLAXO GROUP LTD.), 12 JUL. 2000. SEE THE WHOLE DOCUMENT.	1-3
X	WO 97/03069 A1 (GLAXO GROUP LTD.), 30 JAN. 1997. SEE THE WHOLE DOCUMENT	1-3
X	TIDWELL, R. ET AL 'AROMATIC AMIDINES. COMPARISON OF THEIR ABILITY BLOCK RESPIRATORY SYNCYTIAL INDUCED CELL FUSION AND TO INHIBIT PLASMIN, UROKINASE, THROMBIN, AND TRYPSIN' IN ; JOURNAL OF MEDICINAL CHEMISTRY (1983), 26(2), PP.294-298.	1-3
X	DE 2731039 A1 (AMERICAN HOME PRODUCTS CORP.), 19 JAN. 1978 SEE THE PAGES 1-50	1-3

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

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